This is a digital copy of a book that was preserved for generations on library shelves before it was carefully scanned by Google as part of a project to make the world's books discoverable online.

It has survived long enough for the copyright to expire and the book to enter the public domain. A public domain book is one that was never subject to copyright or whose legal copyright term has expired. Whether a book is in the public domain may vary country to country. Public domain books are our gateways to the past, representing a wealth of history, culture and knowledge that's often difficult to discover.

Marks, notations and other marginalia present in the original volume will appear in this file - a reminder of this book's long journey from the publisher to a library and finally to you.

Usage guidelines

Google is proud to partner with libraries to digitize public domain materials and make them widely accessible. Public domain books belong to the public and we are merely their custodians. Nevertheless, this work is expensive, so in order to keep providing this resource, we have taken steps to prevent abuse by commercial parties, including placing technical restrictions on automated querying.

We also ask that you:

+ *Make non-commercial use of the files* We designed Google Book Search for use by individuals, and we request that you use these files for personal, non-commercial purposes.

+ *Refrain from automated querying* Do not send automated queries of any sort to Google's system: If you are conducting research on machine translation, optical character recognition or other areas where access to a large amount of text is helpful, please contact us. We encourage the use of public domain materials for these purposes and may be able to help.

+ *Maintain attribution* The Google "watermark" you see on each file is essential for informing people about this project and helping them find additional materials through Google Book Search. Please do not remove it.

+ *Keep it legal* Whatever your use, remember that you are responsible for ensuring that what you are doing is legal. Do not assume that just because we believe a book is in the public domain for users in the United States, that the work is also in the public domain for users in other countries. Whether a book is still in copyright varies from country to country, and we can't offer guidance on whether any specific use of any specific book is allowed. Please do not assume that a book's appearance in Google Book Search means it can be used in any manner anywhere in the world. Copyright infringement liability can be quite severe.

About Google Book Search

Google's mission is to organize the world's information and to make it universally accessible and useful. Google Book Search helps readers discover the world's books while helping authors and publishers reach new audiences. You can search through the full text of this book on the web at `http://books.google.com/`

HARVARD UNIVERSITY.

LIBRARY

OF THE

MUSEUM OF COMPARATIVE ZOÖLOGY.

34608

GIFT OF

Alexander Agassiz

October 21, 1909.

19
34,608

gards of F. W. Bancroft

ON THE RELATIVE EFFICIENCY OF THE VARIOUS METHODS OF ADMINISTERING SALINE PURGATIVES

BY
FRANK W. BANCROFT

(From the Rudolph Spreckels Physiological Laboratory of the University of California.)

From
THE JOURNAL OF BIOLOGICAL CHEMISTRY.
Sm Vol. III, No. 3, July, 1907.

ON THE RELATIVE EFFICIENCY OF THE VARIOUS METHODS OF ADMINISTERING SALINE PURGATIVES.

By FRANK W. BANCROFT.

(From the Rudolph Spreckels Physiological Laboratory of the University of California.)

(Received for publication, April 10, 1907.)

In a recent paper Auer[1] has come to the conclusion "that the subcutaneous and intravenous injection of magnesium sulphate and chloride, sodium sulphate, phosphate, and citrate does not produce purgation in rabbits." These results are just the reverse of those arrived at by MacCallum in this laboratory for all these salts except magnesium chloride. Since I had the opportunity of seeing many of the experiments of Dr. MacCallum, and since his death prevents him from stating his methods and results in greater detail and from pointing out why Auer has arrived at different results, I have attempted to supply these deficiencies. Accordingly, I have repeated some of MacCallum's experiments to obtain the quantitative data which he did not consider it worth while to publish, and have also made some additional experiments in which the effects of dosage by mouth and subcutaneously were compared.

TERMS AND METHODS.

Obviously in an investigation of this kind the criterion of purgation is of the first importance. Auer[2] says "by purgation is here understood the passage of soft and unformed feces in amounts exceeding that which normal animals might conceivably pass." In accordance with this definition Auer does not consider that mere increase in the amount of the feces without an increase in fluidity constitutes purgation. MacCallum, on the other hand, considers that both increase in amount and in fluidity of the feces should be taken into consideration in estimating whether purgation has taken place. This difference is partly responsible for the difference in the conclusions of the two authors. Now in this connection it should be pointed out that, as in the rabbit, the feces are usually dry and well formed, and since the action of small doses of weak purgatives is to increase only the *amount* of feces eliminated in a given time, it is essential in such investigations that the *amount* of the feces should be carefully considered.

---

[1] *Amer. Journ. of Physiol.*, xvii, p. 15, 1906.

[2] *Ibid.*, p. 17.

Another and more important difference in the method of experimentation of the two investigators concerns the nature of the control experiments. This difference, I think, is mainly responsible for the difference in conclusions. Auer seems in general not to have kept control animals for each experiment. For, in his paper, it is only on February 15 that he compares the feces of experimental animals with the feces of control animals observed at the same time. In general he seems to have depended for his controls on animals which were not observed at the same time as the experimental animals with which they were compared; and which therefore may have been in a very different condition from that of the experimental animals. Furthermore he does not appear to have attached much weight to the controls which he did keep. Thus, when the feces of the experimental animals are slightly greater in amount or fluidity than the average of his controls he does not conclude that the salts injected have had a slight effect, but seems to think that, as indicated by his definition of purgation, the purgative effect of the salts has been proved only when the result produced is above the maximum of the controls. MacCallum's method of experimentation, when the actual passage of feces was to be observed, was quite different.[1] He always kept controls which were observed ***at the same time*** as the animals experimented upon, and which were treated exactly like the experimental animals in every respect except that no salts were injected into them. The feces passed by the controls and the experimental animals were compared. It was found that the experimental animals passed more feces, and from this it was concluded that purgation had taken place, and that the purgation had been caused by the salts injected. When, in addition, it was found that the feces eliminated by the experimental animals were more fluid than those eliminated by the controls, this fact was also taken to mean that purgation had taken place.

---

[1] MacCallum: *Amer. Journ. of Physiol.*, x, p. 103, 1904; *On the Mechanism of the Physiological Action of the Cathartics. Univ. of Cal. Publications:* Berkeley, The University Press, pp. 11–13, 1906.

The necessity for simultaneous controls is seen when it is remembered that all that the purgatives can do, is to increase the rate with which the feces already present are eliminated. The milder purgatives will cause only an elimination of the feces already present in the large intestine; while the more powerful ones will in addition bring about peristalsis in the caecum and the elimination of fluid feces. Now, as Auer used only small doses of the salts which MacCallum had classed among the weaker purgatives the need for adequate control experiments was even greater than usual. For, the nature of the food, the amount eaten, the time after eating and drinking, exercise, etc., may all affect the amount and nature of the feces in the large intestine. To determine, therefore, whether a small dose of a weak purgative is having any effect it is essential that the animals compared should start with about the same amount of feces in their large intestine, and the only way to insure this is to take similar animals and to treat them alike.

EXPERIMENTAL RESULTS.

My experiments fall naturally into two groups:

1. Those which simply repeated MacCallum's experiments, small doses being used.

2. Those in which the largest possible doses were used, in order to obtain fluid feces.

At the outset I may say that MacCallum's results have been confirmed in every respect. As an example of the experiments where small doses were employed the following may be taken:

Experiment 1. Four rabbits of about the same size and weight were confined in four similar cages. The animals were separated into two pairs. In one pair the same rabbit was always the control, in the other pair one animal was control one day, and the experimental animal on the next. The rabbits had been fed on hay, grain, and vegetables, but during the experiment were fed only on carrots and water, one half of each carrot going to each member of a pair. The purgative used was $\frac{M}{6}$ sodium citrate, which was injected subcutaneously into the dorsal region in the amounts specified in the table. The feces were collected in jars with false bottoms of wire mesh, so that they were never soaked by the urine.

The most significant thing about these results is that *the amount of feces passed during the first 3 to 5 hours after the injection of the citrate, in every case, was more than that passed by the control animal.* This happened even when the total 24-hour feces of the control animal were more than those of the experimental one. The total amount of feces passed by all the experimental animals during these first 3 to 5 hours after injection was 109.33 grams, while that passed by the controls during the same period was only 4.63 grams. Thus, the amount eliminated by the injected animals during these first few hours was 23 times that eliminated by the controls.

Another noticeable effect of the citrate is seen in comparing Rabbits 1 and 2 which were injected on alternate days. In this case the total daily amount was greater for the injected animal on every day except one. The sum of the totals for the injected Rabbits was 156.83, or about 4 times as much as the sum of the totals for the controls (38.26). For quite a while the rabbits passed almost all their feces on alternate days; and that this alternation was due to the citrate and not to accident is indicated by the fact that it immediately disappeared on the fifth and tenth days when no citrate was given. It is evident that a period of constipation follows the purgation due to the citrate.

But although these results appear so clear and convincing, it is still probably worth while to spend some time in pointing out that it is possible by means of an uncritical examination, to make it appear that they mean little or nothing. Thus, when the total amounts or averages of Nos. 3 and 4 are compared they are found to be practically equal. From this it might be concluded that the citrate had had no effect; and if the feces had been weighed only once a day there would have been no escape from this conclusion. What the citrate has done is not to *make* feces, but to *accelerate* their elimination for a few hours after the injection. After that the control animal may catch up again, as happened with both controls on the first day. The total amount of the feces depends,

TABLE I. EXPERIMENT I.

Day.	Hour.	Rabbit 1.		Rabbit 2.		Rabbit 3.		Rabbit 4.	
		Dose of Sodium Citrate.	Feces.	Dose of Sodium Citrate.	Feces.	Dose of Sodium Citrate.	Feces.	Dose of Sodium Citrate.	Feces.
		cc.	gm.	cc.	gm.	cc.	gm.	cc.	gm.
1	12:00 m.	0		15		0		30	
	Next 3¾ hrs.		2.6		24.2		0.0		16.6
	Next 20¼ hrs.		22.65		12.5		30.83		16.93
	Total 24 hrs.		25.25		36.7		30.83		33.53
2	2:05 p. m.	30		0		0		30	
	Next 3 hrs.		7.74		0.0		0.0		5.7
	Next 16 hrs.		18.7		0.0		30.65		22.76
	Next 5 hrs.		0.0		0.0		0.64		0.0
	Total 24 hrs.		26.44		0.0		31.29		28.46
3	2:15 p. m.	0		30		0		30	
	Next 3 hrs.		0.0		7.6		0.0		7.44
	Next 15 hrs.		0.2		21.7		0.84		0.75
	Next 6 hrs.		0.0		3.34		0.06		5.5
	Total 24 hrs.		0.2		32.64		0.90		13.69
4	2:16 p. m.	30		0		0		30	
	Next 3 hrs.		3.55		1.76		0.0		2.55
	Next 18 hrs.		4.9		0.10		0.0		6.77
	Next 4 hrs.		0.05		0.0		0.0		1.3
	Total 25 hrs.		8.50		1.86		0.0		10.62
5	Next 19 hrs.		0.05		0.10		0.0		0.0
6	10:00 a. m.	0		30		0		30	
	Next 3 hrs.		0.0		0.14		0.17		7.58
	Next 21 hrs.		10.5		0.03		0.0		6.6
	Total 24 hrs.		10.5		0.17		0.17		14.18
7	11:00 a. m.	30		0		0		30	
	Next 3 hrs.		1.9		0.0		0.0		4.8
	Next 18 hrs.		19.35		0.0		32.29		0.0
	Total 21 hrs		21.25		0.0		32.29		4.8
8	9:10 a. m.	0		30		0		30	
	Next 5 hrs.		0.0		13.43		0.0		5.2
	Next 19 hrs.		0.3		13.4		8.2		0.2
	Total 24 hrs.		0.3		26.83		8.2		5.4
9	10:20 a. m.	30		0		0		30	
	Next 4 hrs.		0.3		0.1		0.0		0.6
	Next 25 hrs.		4.4		0.05		7.8		9.9
	Total 29 hrs.		4.3		0.15		7.8		10.5
10	Next 26 hrs.		0.6		0.1		11.2		3.2
	Totals		97.39		98.55		122.68		124.38
	Average 24 hrs.		9.74		9.85		12.27		12.44

in the first place, upon the amount and the bulkiness of the food eaten; and only secondarily on the amount of water in the feces. It is only by increasing the water that moderate doses of purgatives can increase the total amount of feces eliminated in an experiment of several days' duration. We should expect, however, that the amount of water in the feces should be influenced by the citrate, and the reason why the results do not show it is because No. 3 for some unknown reason had the diarrhoea. After the first day the feces of all the rabbits were always unusually moist whenever they were eliminated in considerable quantities. This may have been due to the citrate in Nos. 1, 2 and 4, and to some other unknown cause in No. 3; or it may have been due to the carrots in all four rabbits. At any rate our results do not allow us to conclude that the citrate has increased the amount of water in the feces. In later experiments, however, it will be shown that subcutaneous injection of saline purgatives does produce more fluid feces.

A further consideration of the rate of the elimination of feces will show how absolutely essential it is to have adequate control animals. The total amount of feces eliminated by all four rabbits during the 240 hours of observation was 443.0 grams, giving an average rate of 0.46 grams per rabbit per hour. The 109.33 grams eliminated by the injected animals during the first 3 to 5 hours after the injections were eliminated in 27.75 hours; which gives an hourly rate of 1.97 grams per rabbit. Were it not for the controls we would be forced to conclude that the citrate had accelerated the elimination only about 4 times, while a comparison with the controls shows us that the rate has been accelerated 23 times. The explanation appears to be that normally the feces are not passed at a uniform rate, but much more rapidly at certain times of day than at others; and the time of day at which the injections were made was one during which ordinarily but little feces would be passed. But this would not have been realized if adequate controls had not been kept.

Finally, the last thing in the results to which I wish to call attention is the effect of the food on the amount of the feces. Before the experiment was begun the rabbits had been fed largely on hay, which contains much more cellulose than the carrots fed during the experiment. The cellulose is not digested and constitutes the main bulk of the feces. So we should expect much less feces on a diet of carrots than on a diet composed largely of hay. The evident decrease in the daily elimination during the course of the experiment is due to this change of diet.

The effect of the character of the food on the amount of feces passed, and so indirectly upon the purgation is strikingly shown when the results just discussed are compared with those of the next experiment.

Experiment 2. The same rabbits as in Experiment 1, but they have been fed hay, grain, and water for several days. The same diet is continued during the experiment. $\frac{M}{6}$ sodium citrate is given to No. 1 by mouth, and to No. 2 subcutaneously.

TABLE II. EXPERIMENT 2.

Day.	Hour.	No. 1, 1580 gm. per os.		No. 2, 1501 gm. subcut.		No. 3. 1697 gm. Control.	No. 4. 1621 gm. Control.
		Dose of Sodium Citrate.	Feces.	Dose of Sodium Citrate.	Feces.	Feces.	Feces.
		cc.	gm.	cc.	gm.	gm.	gm.
1	2:10 p. m.	30		30			
	First 1 hr.		4.9		13.8	8.3	2.4
	First 3 hrs.		13.8		21.6	14.9	5.9
	Next 15½ hrs.		17.4		46.5	57.4	19.5
	Total 18½ hrs.		31.2		68.1	72.3	25.4
2	9:20 a. m.	30		30			
	First 1 hr.		23.1		0.0	2.3	4.3
	First 4½ hrs.		27.4		8.7	23.8	5.5
	Next 23½ hrs.		2.2		23.9	66.7	35.3
	Total 28 hrs.		29.6		32.6	90.5	40.8
3	1:40 p. m.	30		30			
	First 1 hr.		13.6		8.8	7.8	8.8
	First 4 hrs.		23.9		18.2	24.8	18.1
	Next 16 hrs.		29.1		0.5	36.2	32.0
	Total 20 hrs.		53.0		18.7	61.0	50.1
4	10:00 a. m.	30		30			
	First 1 hr.		2.8		10.0	2.1	13.4
	First 4 hrs.		14.6		21.0	16.1	32.9
	Next 24 hrs.		69.8		30.4	62.3	60.1
	Total 28 hrs.		84.4		51.4	78.4	93.0
	Totals						
	First 1 hr.		44.4		32.6	20.5	28.9
	First 3-4½ hrs.		79.7		69.5	79.6	62.4
	Daily Totals		198.2		170.8	302.2	209.3

In this experiment I used the same rabbits employed for Experiment 1, but the diet had increased the average daily feces from 11.1 grams in Experiment 1 to 54.4 grams. This additional amount of feces almost entirely obliterated any effect that might be due to the citrate. It is only by comparing the totals that it can be seen that in spite of the fact that the controls are larger animals, and pass more feces, yet during the first hour after the administration of the citrate the experimental animals passed the greater amount of feces. It should be noted, however, that there is no great difference, in this case, between the effects of the citrate when given by mouth or subcutaneously. But this diminution in the effect of the purgative with the more bulky diet should not surprise us. The rabbits are now constantly passing pellets. On one day hourly observations were made on all four rabbits from 10:00 a. m. to 4:00 p. m., and there was only one hour for one of the rabbits during which no feces were passed. On the average a pellet was passed every 6 minutes throughout the 24 hours, and with such an output it is not surprising that the effects of small doses of sodium citrate might be hard to detect. But that decided purgation is possible, even on a diet of hay and grain, will be shown in the following experiments in which much larger doses were given.

EFFECTS OF MAXIMAL DOSES.

In this second series the attempt was made to obtain fluid feces. The food given was usually hay and grain. In some cases other food was given, but in every case the same food was given to both control and experimental animals. Sodium citrate, sodium sulphate, and barium chloride were given both by mouth, subcutaneously, intravenously, and intra-abdominally. It was found possible to obtain fluid feces by means of all four methods of administration. They could be obtained in most cases when the purgatives were given by mouth; but the doses required were enormous. When, however, the same doses were given subcutaneously or intravenously the rabbits were often killed before fluid feces were obtained. In these fatal cases post mortems showed that the salts had acted as purgatives, but that their action had been cut short by death.

EFFECTS OF SODIUM CITRATE.

The above statements were particularly true for this salt. Divided doses of from 50 to 120 cc. of $\frac{M}{6}$ sodium citrate given subcutaneously or intra-abdominally killed the rabbits in from 3 to 9 hours, according to the rapidity with which the solutions were injected. When given by mouth 100 to 250 cc. given at the rate of about 50 cc. per hour produced fluid feces in about one-third of the experiments. When the citrate was given in other ways than by mouth the rabbits survived a dose of 100 cc. or more in only one case. In this case 180 cc. were given, and, as was to be expected, it had the same effect as when given by mouth; causing after 6 hours the elimination of perfectly fluid and unformed feces in considerable quantities. In this experiment the animal that was treated by mouth received 250 cc. of citrate during 5 hours, but produced only pasty and sticky feces that were still formed. The feces of the control were dry and hard.

Post mortems were made on the animals that died, and in almost every case it was evident that if the intestines had continued to function for a little longer the fluid feces which had replaced the formed pellets usually found in the large intestine would have been extruded. It is thus seen that while it is much easier to obtain fluid feces by giving sodium citrate by mouth than by giving it subcutaneously or intra-abdominally this difference in results is due to the increase in toxicity when given in these latter ways, and not because the salt has a different action on the digestive tract.

EFFECTS OF SODIUM SULPHATE.

In these experiments, also, the main attempt was to obtain fluid feces, and the experiments were not arranged to show the greatest differences in the weight of the feces of control and experimental animals; but in spite of this disadvantage, striking quantitative results were obtained. These results are shown in the following summaries:

These summaries show that in spite of the fact that the injected animals got such large doses that they were seriously injured and often killed by them, thus of course diminishing the activity of the digestive tract, the injected animals passed on the whole much larger quantities of feces than the controls. Thus, the rabbits that were injected subcutaneously passed about 3½ times as much feces as the controls; while those that were injected intravenously passed about 10 times as much. These results show very clearly that the subcutaneous and intravenous administration of sodium sulphate increases markedly the amount of feces eliminated for some time after. When given by mouth this salt increases the amount of feces to an even greater extent.

TABLE III.

SUMMARY OF SUBCUTANEOUS INJECTIONS OF SODIUM SULPHATE.

Date.	Duration of Experiment.	Dose of Na_2SO_4.	Weight of Feces in Grams.		
			Control.	Dose by Mouth.	Dose subcut.
Jan. 1	19 hrs.	110 cc. m/2	18.6	8.3	62.4
" 7	20 "	80 cc. m/2	0.5	56.4	48.3
" 7	2 "	80 cc. m/2	0.3	20.2	2.3*
" 8	23½ "	60 cc. m/2	0.9	14.3	0.4*
" 11	18 "	70 cc. m/2	0.2	87.5	24.0
" 11	21 "	80 cc. m/2	0.0	37.0	25.5
" 12	20 "	250 cc. m/6	29.6†	70.0	11.0‡
Totals			50.1	293.7	173.9

* Rabbit died during experiment.
† Average of four controls.
‡ Rabbit very sick.

TABLE IV. SUMMARY OF INTRAVENOUS INJECTIONS OF SODIUM SULPHATE.

Date.	Duration of Experiment.	Dose of Na_2SO_4.	Weight of Feces in Grams.		
			Control.	Dose by Mouth.	Dose Intravenous.
Jan. 13	5 hrs.	520 cc. m/6	0.2†	51.1	9.8*
" 14	8 "	501 cc. m/6	0.0		‡15.8*
" 16	23 "	409 cc. m/6	6.2		72.8
" 18	6 "	302 cc. m/6	1.9		31.0
" 19	4 "	267 cc. m/6	4.5		3.4*
Totals			12.8		132.8

* Rabbit died.
† Average of four controls.
‡ Injection into abdomen.

FLUIDITY OF THE FECES.

In addition to the increase in the amount of feces, the injection of sodium sulphate also increases the proportion of water contained in them. This proportion was not measured quantitatively, so the data are not so satisfactory. In three of the experiments with subcutaneous injections the injected animals passed pasty or semifluid feces, while none of the controls did so.

With intravenous injection, however, the effect of the salt on the fluidity of the feces was most clearly shown. In these experiments the rabbits remained tied down on the board for the whole of the 4 to 8 hours during which the salt was given. They were covered with cotton batting to keep their temperature up. A warmed $\frac{M}{6}$ solution of sodium sulphate was allowed to flow from a burette continuously into the marginal vein of the ear at the rate of from 30 to 50 cc. per hour. In these experiments there was a regular progressive increase in the fluidity of the feces. At first there were well formed pellets, hard and dry. After from four to six hours these pellets began to be more moist. At first they were hard and well formed, but moister than usual on the surface, as if the moisture had entered the intestine after the pellets had been formed. Later the pellets became moist clear through, and soft. Later still they were pasty and semifluid, the masses not well formed at all, and so soft that after they had been collected the masses could hardly be distinguished. Finally, in some cases, just as the first really fluid feces were being passed the animal died. In these cases the post mortem showed that if the intestines had continued to act as they had been doing for a little longer fluid feces would have been obtained. For in these cases, the lower part of the large intestine, which usually contains hard well-formed pellets, was filled for distances of from 5 to 20 centimeters with perfectly unformed and fluid feces. In all the experiments the controls never once showed such a regular increase in the fluidity of the feces. These facts show very conclusively that the *intravenous injection of sodium sulphate increases markedly the amount of water in the feces.*

COMPARISON WITH ADMINISTRATION BY MOUTH.

When now we come to compare the effect of giving sodium sulphate by mouth with the results just described, a decided difference is observed. Fluid feces can easily and almost invariably be obtained by giving sodium sulphate by mouth. From 60 to 110 cc. of $\frac{M}{2}$ sodium sulphate or 250 to 300 cc. of the $\frac{M}{6}$ solution caused an elimination of fluid feces in every case except one, and in no case had any injurious effect on the rabbit. Why this difference? In answering this question it is essential that the *normal anatomy and physiology of the rabbit's digestive tract should be kept in mind.* The food is ordinarily very bulky, containing much cellulose, and the digestive tract is adapted to these conditions. The stomach is large and is never empty; and between the small and the large intestine is the enormous caecum, which is always filled with rather fluid, partially digested material. The food passes very slowly through the digestive tract. Thus, when I fed carrots, the feces became reddish in color, but this color was not decided until the carrots had been fed for several days and persisted for several days after the diet had been changed. When a control animal is killed the greater part of the large intestine is usually found to contain well-formed pellets, and it is only within the caecum or its immediate vicinity, that any considerable quantity of fluid feces is seen. When sodium sulphate is given by mouth the same regular increase in fluidity described for intravenous injections is obtained, and it takes about 6 hours before fluid feces are obtained. In view of these facts, then, it is obvious that the fluid feces have not been produced so much by the transformation of solid feces in the large intestine, as by the rapid conveyance of fluid feces from the caecum to the exterior. Accordingly unusual activity of the large intestine, and particularly of the caecum, would appear to be the *sine qua non* for the elimination of fluid feces. As a matter of fact when fluid feces were obtained, the peristalsis of the caecum was sometimes so violent that it could easily be seen through the muscles, skin, and hair of the abdomen.

We may now return to the explanation of why the sodium sulphate, given by mouth, is so much more effective in producing fluid feces. The reasons for this are mainly three:

1. When given by mouth the salt solution is not rapidly absorbed into the circulation, but is passed down into the caecum. Thus the solution distends this organ, and dilutes its contents, thus tending by its water and bulk alone to make the feces more fluid, and to produce peristalsis of the caecum.

2. When injected subcutaneously the solution is not rapidly absorbed into the circulation, and so does not reach the intestine in as great concentration as when given by mouth.

3. When injected intravenously it is diluted by the blood and acts all over the body, so that only a small portion reaches the intestine. But more important than this is the fact that it acts as a diuretic, and is rapidly eliminated by the kidneys.

The evidence for these three reasons will be presented in order:

1. Post mortems made six or seven hours after the solution has been given by mouth show the caecum very much distended with unusually fluid feces. This fluid must have come directly from that introduced into the stomach; for if it had been absorbed and secreted again it must have been in circulation for a while, and in that case it would have caused diuresis, which did not take place. That the mere volume of the solution has had considerable effect is shown by the fact that 350 cc. of tap water given by mouth caused the elimination of pasty and semifluid feces.[1]

2. That absorption is slow when sodium sulphate is injected subcutaneously is shown by the persistence for several days of the jelly-like oedematous mass that forms about the region of the injection. An interesting behavior of this mass was noted when $\frac{M}{2}$ sodium sulphate was injected into the dorsal region. When this was done the mass would form as usual, and then, apparently acted on by gravity, would slowly travel down the sides of the rabbit until it came to rest in the midventral line where it would persist for several days. This migration usually took 4 or 5 hours to complete. Post mortems showed a slight inflammation in the region of the swelling.

3. The rapid excretion of intravenously injected sodium sulphate is easily shown. The rabbits thus treated were constantly urinating, while the controls, and rabbits receiving the salt by mouth urinated but rarely. In one experiment, in spite of con-

---

[1] The most striking result produced by the water was the phenomenon, already noted by Claude Bernard, that pronounced trembling and shaking and muscular twitching was produced. This shaking was much more pronounced than similar phenomena obtained by the subcutaneous injection of sodium citrate, and was not obtained at all with larger doses of sodium citrate and sodium sulphate given by mouth.

siderable loss of urine by evaporation and in other ways, 150 cc. of the 267 cc. injected were recovered in the urine. That this urine carried with it much of the sodium sulphate introduced is self-evident, but direct evidence for it was also afforded by the oedematous jelly-like masses in the vicinity of the kidneys, and by the inflammation of kidneys and bladder.

This fact of the exceptional effectiveness of sodium sulphate when given by mouth and the explanations of the same all go to show what was already well known to us by MacCallum's investigations, that the mechanism for the production of purgation is located in the walls of the digestive tract.

EFFECTS OF BARIUM CHLORIDE.

This salt, as has been pointed out by MacCallum in a number of papers, is the most energetic of the saline cathartics. He says:[1] "For anyone to convince himself that a salt may act as a purgative when injected subcutaneously or intravenously it is only necessary to introduce a small amount of $BaCl_2$ into the blood or under the skin of a rabbit. The evacuation of large quantities of semifluid feces and the violent intestinal movements leave no room for doubt as to the action of the salt. The fact that the intravenous and subcutaneous administration of this salt as a purgative by veterinarians is in general use should be sufficient proof." Auer did not test the purgative effect of barium chloride. I have made a few experiments with this salt in order to compare the effects of *per os* and *subcutaneous* administration of a powerful saline purgative.

It has been shown that with the mild purgative sodium sulphate acts better by mouth, because the fluid is not rapidly absorbed from the digestive tract, and so has time to accumulate in the caecum, which it distends, and the contents of which it dilutes. It acts less strongly when given intravenously because it is rapidly excreted by the kidneys. Thus in both cases the sodium sulphate reaches the purgative mechanism in the intestines, but on account of the slow absorption from the intestines, it remains in contact with this mechanism longer when given by mouth than when given intravenously; and since this is a mild purgative a long contact is essential. With barium chloride, however, the conditions are quite different. Purgation can be obtained with such small doses that the bulk of the fluid introduced into the digestive tract cannot be of consequence in aiding purgation. Furthermore, it is very probable that it is not rapidly eliminated by the kidneys, for MacCallum has shown[1] that intravenous doses of 1 cc. of $\frac{M}{8}$ barium chloride stop the secretion of the urine. For these reasons, then, it might be expected that barium chloride would be more effective when given subcutaneously than when given by mouth, and such I have actually found to be the case.

---

[1] *On the Mechanism of the Physiological Action of the Cathartics. Univ. of Cal. Publications:* Berkeley, The University Press, pp. 20–21, 1906.

Subcutaneous doses of 2 cc. of $\frac{M}{8}$ barium chloride never failed to cause the elimination of fluid feces within two hours. The action was very regular. Feces began to be passed within a few minutes after the injection. At first the pellets were hard and dry, but after about 30 to 40 minutes they were still hard but were covered with a good deal of surface moisture. The amount of this moisture increased, and the pellets became softer, until finally the fecal masses were entirely unformed. They were rather lumpy, some parts being pasty, while others were so fluid that they flowed through wire netting with millimeter meshes, and wet the hair about the anus. These feces were much more fluid than those of any rabbits that I have seen that have not had purgatives, so that no matter what definition of purgation be adopted it must be concluded that barium chloride does purge when given subcutaneously.

When given by mouth the action of barium chloride takes longer in manifesting itself, and is much less constant. In two of the four experiments no fluid feces were obtained, the pellets remaining distinct. In one experiment the feces were entirely unformed and mushy, but were not fluid enough to run through the millimeter meshes. In only one case were the feces really fluid, but in this case they were more fluid than any which were passed after the subcutaneous administration of barium chloride. All the rabbits receiving barium chloride subcutaneously died either during the experiment, or an hour or two after; while only one of the rabbits that were treated by mouth died, and that one only after many hours. The quantitative data of the experiments are contained in the following summary.

---

[1] *Journ. of Exp. Zoöl.*, i, p. 186, 1904.

TABLE V. SUMMARY OF EXPERIMENTS WITH BARIUM CHLORIDE.

Date.	Duration of Experiment.	Dose of $\frac{M}{6}$ $BaCl_2$	Weight of Feces in Grams.		
			Control.	Dose by Mouth.	Dose subcut.
Jan. 4	2 hrs.	4 cc. divided	0.0	88.2	45.8
Feb. 7	1 hr. 25 min.	2 c .	9.2	13.5	30.3
" 25	3 hrs. 15 min.	2 cc.	0.5	28.9	29.1
" 26	1 hr. 35 min.	2 cc,	0.5	21.5	42.6
Totals			10.2	152.1	147.8

DISCUSSION OF RESULTS.

It has been shown, as may be seen in the following summary, that the subcutaneous or intravenous injection of sodium citrate, sodium sulphate, and barium chloride brings about a passage of feces from 1.3 to 23 times the amount passed by the controls.

SUMMARY OF THE TOTALS.

Purgative.	Usual Dose.	Food.	Usual Duration of Experiment.	Grams of Feces Eliminated by Experimental Animals for each Gram Passed by Controls.		
				Control.	Dose by Mouth.	Dose sub-cut. or Intraven.
Sodium citrate	30 cc. m/6	carrots.	4 hrs.	1		23.0
Sodium citrate	30 cc. m/6	hay, etc.	4 hrs.	1	1.6	1.3
Na_2SO_4	80 cc. m/2	mixed.	20 hrs.	1	5.9	3.5
Na_2SO_4	400 cc. m/6	"	6 hrs.	1	3.9	10.4
$BaCl_2$	2 cc. m/6	"	2 hrs.	1	14.9	14.5

When given in large doses, the subcutaneous or intravenous administration of all these salts also causes the passage of *more fluid* feces than those passed by the controls. These results confirm in every respect the conclusions arrived at by MacCallum. Our conception of purgation, then, is that the mechanism for this process is located in the wall of the digestive tract. This mechanism consists of both muscles and glands the stimulation of which produces peristalsis and secretion. This stimulus may be supplied, among other things, by the purgative salts. One method of demonstrating this stimulation which MacCallum has described, is to open the abdomen and observe the peristalsis after the injection of the purgative salts. Auer has confirmed these observations of MacCallum, except for magnesium sulphate. But as he has been unable to demonstrate any increase in the feces eliminated after injection of these salts, Auer concludes "Peristalsis and purgation are not synonymous terms; increased peristalsis may occur during constipation." According to the conception of purgation here outlined the increased peristalsis shows that at least part of the purgative mechanism has been stimulated. But in order that this stimulus may result in the increased elimination of feces it must be kept up for a considerable time. Consequently it is easier to demonstrate increased peristalsis than increased elimination of feces. I have found that fluid feces will be produced by barium chloride after it has been in contact with the purgative mechanism for an hour and a half. Sodium sulphate, which is a much weaker purgative, requires, under the most favorable circumstances, not only 100 or 200 times as strong a dose, but *six* hours in which to produce fluid feces. This shows us that *time* is an essential factor in the process. Thus, in order to be effective in the elimination of feces the salts must not only be brought in contact with the purgative mechanism, but *they must be kept there for a certain time*. This principle should always be kept in mind in considering the different effects produced by the different methods of administering saline purgatives.

Having discussed the reasons for the difference in the results of MacCallum and Auer, I might close here were it not for the emphasis that Meltzer and Auer have laid upon MacCallum's statement that magnesium sulphate acts as a purgative when given subcutaneously.

ACTION OF MAGNESIUM SULPHATE.

In a series of papers on the action of magnesium salts Meltzer and Auer have found that in all cases these salts have a narcotic or inhibitory action, and never a stimulating effect. On the other hand they say that MacCallum's results with saline purgatives, including magnesium sulphate, lead to the conclusion that this salt does have a stimulating effect. Speaking of MacCallum's work Meltzer and Auer[1] say: "Here we have, then, a pronounced theory supported by experiments that purgatives, magnesium sulphate included, produce peristalsis by increasing the sensitiveness of nerve and muscle of intestines; in other words, here we seem to have an instance in which magnesium salts do not inhibit but stimulate activity." Now in this quotation we have one example of a misconception that runs all through their paper. They everywhere seem to consider magnesium sulphate and magnesium salts as synonymous terms; and seem to think that MacCallum considered the purgative action of magnesium sulphate due to the magnesium which it contains. Nothing could be farther from the truth. MacCallum was very familiar with the way in which magnesium inhibits intestinal peristalsis. In fact he was the discover of this inhibition, and has mentioned it in a number of papers.[2] Concerning the purgative action of magnesium sulphate he says in his last paper,[3] concluded but a short time before his death: "This salt of course acts as a purgative because it is a sulphate and not on account of the presence of magnesium. As shown later on, magnesium chloride has an effect quite opposite to this."

Meltzer and Auer do not mention any of MacCallum's results on the inhibitory effect of magnesium in their paper on the relation of magnesium salts to peristalsis, in spite of the fact that these results are exactly in accord with their main contention that the effect of these salts is always an inhibitory or narcotic one. On the contrary, starting with MacCallum's statement that magnesium sulphate acts as a purgative when given subcutaneously, they lead one to believe that MacCallum thought that in this case magnesium stimulates peristalsis.

---

[1] *Amer. Journ. of Physiol.*, xvii, p. 314, 1906.

[2] MacCallum: *Amer. Journ. of Physiol.*, x, p. 259, 1904; also, *Arch. f. d. ges. Physiol.*, civ, p. 425, 1904; *Journ. of Exp. Zoöl.*, i, p. 179, 1904; *Univ. of Cal. Publications*, Physiology, ii, p. 47, 1905; this *Journal*, i, p. 339, 1906; *On the Mechanism of the Physiological Action of the Cathartics. Univ. of Cal. Publications:* Berkeley, The University Press, p. 38, 1906.

[3] *On the Mechanism of the Physiological Action of the Cathartics. Univ. of Cal. Publications:* Berkeley, The University Press, p. 21, 1906.

As MacCallum has often stated, the theoretical ideas upon which his conception of purgation was based are due to Loeb.[1] In a series of papers, the first of which was published in 1899, Loeb[2] found that in producing muscular twitchings and some other phenomena sodium and barium salts were particularly effective, and were counteracted by calcium and magnesium salts. On account of the counteracting effect of calcium the sodium salts that were most effective were those that precipitate calcium. For this reason sodium sulphate is more effective than sodium chloride, because it not only adds sodium but takes away calcium from the solution. Similarly, magnesium sulphate will remove calcium while it adds magnesium. Now since calcium inhibits more strongly than magnesium, the addition of magnesium sulphate should have something of a stimulating effect, not because of the magnesium but because of the SO_4-ion which precipitates the calcium. In this way, then, the purgative effect of magnesium sulphate is explained; and it can be seen at once that, according to this view, magnesium sulphate should be considered a rather unsatisfactory purgative, as it contains both stimulating and inhibitory components.

It is of course a fundamental precaution in interpreting the effect of any salt, to consider the possibility of either ion having produced the effect, and Meltzer and Auer have on other occasions been careful in taking this precaution. In the paper under discussion, however, they have on several occasions failed to do so. Thus, when testing the effect of magnesium salts in stopping the peristalsis caused by barium chloride they find in one experiment that magnesium sulphate stops the peristalsis, and conclude from this that magnesium salts do inhibit the peristalsis. Now while this conclusion is right it is not justified by the fact, for it is well known that magnesium sulphate reacting with barium chloride will produce barium sulphate which is insoluble. The barium would thus be removed from solution and could no longer produce its characteristic effect. The injection of magnesium chloride, on the other hand, which was also tried by the authors, does show that the magnesium inhibits the peristalsis.

---

[1] *Univ. of Chicago Decennial Publications*, x, p. 10, 1902.

[2] *Festschrift für Fick*, Braunschweig, p. 99, 1899.

In conclusion, then, it may be stated that a re-examination of the effect of intravenous and subcutaneous injection of sodium citrate, sodium sulphate, and barium choride has shown that these salts markedly increase the amount of feces eliminated, and also, when given in larger doses, markedly increase the fluidity of the feces. These results confirm in every respect the conclusions of MacCallum. The reasons why Auer, and Meltzer and Auer have been unable to confirm this result seem to be: (1) they used only the milder purgatives mentioned by MacCallum, and (2) in using these they did not keep adequate controls and thus failed to notice the increase in the amount of feces which they were probably getting.

SUMMARY.

1. In any experiments dealing with the quantity and character of the feces eliminated it is absolutely essential that the feces of the experimental animals should be compared with those of control animals kept at the same time and treated in the same way as the experimental animals, except of course that no salts are given to them. The neglect of this precaution is largely responsible for the different results arrived at by Auer and MacCallum.
2. When small doses of mild purgatives are given a bulky diet will sometimes largely mask any effect that might be due to the purgative. In such experiments, therefore, a more concentrated diet should be given.
3. The subcutaneous injection of small doses of sodium citrate was found to increase the feces eliminated for the next 3 to 5 hours to 23 times the amount eliminated by the controls.
4. The intravenous injection of maximal doses of sodium sulphate was found to increase the feces 10 times.
5. The subcutaneous injection of 2 cc. of barium chloride was found to increase the feces eliminated for the next two hours 14½ times.
6. Large subcutaneous or intravenous doses of all three of these salts make the feces eliminated unusually moist. After barium chloride the feces even become partially fluid.
7. Fluid feces can be more easily obtained with sodium citrate when it is given by mouth because it usually takes more than

100 cc. of an $\frac{M}{6}$ solution to produce fluid feces, and this amount is almost always fatal when given subcutaneously.

8. With sodium sulphate fluid feces are more easily obtained when the salt is given by mouth because:

a. It is but slowly absorbed from the digestive tract, and so is passed on down into the caecum which it distends and the contents of which it dilutes. It thus remains in contact with the walls of the digestive tract for a long time and has a chance to affect the mechanisms for peristalsis and secretion which are contained in the walls.

b. It is but slowly absorbed from the subcutaneous tissue, and so never reaches the walls of the digestive tract in sufficient concentration to produce its maximum effect.

c. When introduced into the circulation it acts as a diuretic and is thus rapidly eliminated and never reaches the intestines in sufficient concentration and for a long enough time to produce its maximum effect before it has killed the rabbit.

9. With barium chloride fluid feces are more easily obtained when the salt is given subcutaneously than when it is given by mouth.

10. In considering the effect of any salt it should always be borne in mind that the effect may be due to the activity of either anion or cation. Magnesium sulphate acts as a purgative on account of its anion.

11. All of these results go to show that MacCallum's conclusions are correct: The mechanism for causing purgation is in the intestinal walls and is stimulated whenever any saline purgative reaches it in sufficient concentration no matter in what way that purgative may have been introduced into the body.

PRESS OF WILLIAMS & WILKINS COMPANY
BALTIMORE